REMARKS

Claims 114-119 and 123-132, and 135-141 were pending in the present application. Claims 135, 136, and 138 have been amended to specify Nogo functional activities.

New claims 142 to 146 have been added. Support for the amended claim recitations and for the new claims can be found in the application as originally filed as set forth in the chart below.

Claim	Support
135, 136, 138	p. 11, *ll.* 20-30
142	p. 17, *ll.* 6-11
143	Section 5.2, beginning at p. 21
144	p. 21, *ll.* 20-30
145 and 146	Section 5.2, beginning at p. 21; p. 11, *ll.* 11-16; p. 25, *ll.* 7-8 and 30-33

No new matter has been introduced by these amendments. Claims 114-119 and 123-132, and 135-146 will be pending upon entry of the present amendments.

1. THE REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, SHOULD BE WITHDRAWN

1.1 THE REJECTION UNDER 35 USC § 112, FIRST PARAGRAPH, BASED ON NON-ENABLEMENT SHOULD BE WITHDRAWN

Claims 115-116, 118-119, 123-125, 136, and 138-141 are rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly fails to provide enabling support for Nogo protein fragments that do not inhibit fibroblast spreading,[1] or for Nogo protein fragments that are antigens of antibodies for which no *in vitro* or *in vivo* data has been provided, or for nucleic acids encoding these fragments. These allegedly non-enabled Nogo protein fragments include, *e.g.*, amino acids 975-1163 of SEQ ID NO:2, also referred to as Nogo C. Applicants appreciate the Examiner's statement that, *e.g.*, SEQ ID NO:2, SEQ ID

[1] For ease of reference, the ability of Nogo proteins and fragments to inhibit fibroblast spreading or neurite outgrowth will be referred to as "inhibitory activity."

NO:29, residues 1-171 of SEQ ID NO:2 fused to residues 975-1163 of SEQ ID NO:2, and residues 1-172 of SEQ ID NO:29 fused to residues 990-1178 of SEQ ID NO:29, are enabled (Office Action dated December 21, 2006, p. 3).

The Examiner's position is that only proteins with inhibitory activity are useful and that therefore only these proteins are enabled. In their previous responses, Applicants had submitted evidence showing that the application as filed enables a patentable use for Nogo proteins and fragments thereof without inhibitory activity. In particular, Applicants had provided evidence that these proteins can be used to generate antibodies, which in turn are useful for the detection and measuring of Nogo proteins, including such Nogo proteins with inhibitory activity. The Examiner rejects Applicants arguments because allegedly antibodies raised against Nogo proteins without inhibitory activity would be expected to bind only to Nogo protein without inhibitory activity, and therefore cannot be used to purify Nogo protein with inhibitory activity. In particular, the Examiner contends that the antibodies to inactive fragments such as Nogo C "would most likely bind to the inactive fragments themselves, rather than to the full-length Nogo protein" (Office Action of December 21, 2006, p. 5). The Examiner contends that hexapeptides are sufficient to make antibodies (citing Hopp and Woods[2]), and that therefore "antibodies raised against the useless fragments would be expected to have considerable cross-reactivity with other proteins, abrogating any possible use in purifying full-length Nogo." *Id.* Applicants respectfully disagree for the reasons summarized below and set forth in detail in Applicants' previous responses.

The teachings of Hopp and Woods have been discussed previously (see, *e.g.*, Amendment of October 4, 2006, p. 20, Section 2.1.(3)). Briefly, Hopp and Woods do *not* teach that a hexapeptide is sufficient to make an antibody, but rather that the point of highest local average hydrophilicity, which may be six amino acids long, in a protein correlates with the antigenic determinant of that protein. Thus, not just *any* six amino acids constitutes an epitope, but rather ones that constitute a point of highest local average hydrophilicity. Consequently, a hydrophilicity analysis according to Hopp and Woods can be used to locate antigenic determinants in the Nogo protein.

Nogo proteins without inhibitory activity, such as Nogo C, can be used to generate antibodies that bind to Nogo C and cross-react with full length Nogo because of the shared

[2] 1981, PNAS 78:3824, ("Hopp and Woods," attached as Exhibit E to the response of December 28, 2005)

amino acid sequences of these different forms of Nogo (see Preliminary Statement in the Amendment of October 4, 2006). It is noted that antibodies against Nogo C, for example, are expected to cross-react with Nogo A, for which inhibitory activity has been demonstrated, because these two isoforms of the Nogo gene share one exon in common.

The Examiner's contention that antibodies to "inactive fragments such as Nogo C" would fail to bind to Nogo A (which shares an exon with Nogo C) is wholly unsupported and speculative, and is contrary to common knowledge and usage in the art wherein, for example, even a short synthetic peptide is commonly used as immunogen to generate immunospecific antibodies to a full-length protein containing the peptide sequence (See "Synthetic Peptides," pages 72-77, in: Antibodies A Laboratory Manual, Harlow and Lane (eds.), 1988, Cold Spring Harbor Laboratory Press; attached as Exhibit A; "Harlow and Lane").[3] This common usage of peptide immunogens in the art, and the Examiner's misperception regarding the teachings of Hopp and Woods, discussed above, also show the incorrectness of the Examiner's contention that antibodies raised against Nogo C would have considerable cross-reactivity with other proteins, abrogating any possible use in purifying Nogo A. Rather, it is expected that antibodies recognizing Nogo A would be obtained when using Nogo C as an immunogen (*e.g.*, claim 140), since Nogo A and Nogo C share a sequence of 188 amino acids (p. 12, *ll.* 24-28), which is much larger than the short peptides commonly used to generate antibodies to a full-length protein (see Harlow and Lane at p. 76). Similarly, the other sequences specified in claim 140 are also much larger than the short peptides commonly used to generate antibodies to a full-length protein (see Harlow and Lane at p. 76). Since these fragments are fragments of Nogo A, antibodies against these fragments would be expected to recognize Nogo A. Applicants further point out that the antibodies need not have use in purifying Nogo A, since detecting and measuring Nogo A in assays is also a patentable use that is expected to be exhibited by the generated antibodies. Moreover, while an antibody that binds *both*, Nogo protein with and without inhibitory activity, may not be sufficient by itself to specifically purify Nogo protein with inhibitory activity, such antibodies still have enabled utility as discussed in Applicants' previous responses and as summarized below.

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[3] It is to be noted that to enable detection and measuring of Nogo A, the antibody need not recognize native Nogo A, but it is useful even if it recognizes only denatured Nogo A. As but one example, an anti-Nogo C antibody that recognized only denatured Nogo A can be used in an assay to detect and measure only Nogo A as follows: Nogo A could be immunoprecipitated with an antibody to Nogo A, and then detected on a Western blot with the anti-Nogo C antibody.

The same argument as for Nogo C above holds true for Nogo proteins with more than 90%, or more than 95%, respectively, amino acid sequence identity to Nogo A or Nogo B (claims 115, 116, 118, and 119). Whether or not these Nogo proteins have inhibitory activity, they can be used to generate antibodies that are expected to recognize Nogo A and Nogo B, respectively, because of the high degree of sequence identity. Consequently, these antibodies can be used to measure and detect Nogo A and Nogo B, for which inhibitory activity has been demonstrated (rat Nogo A and Nogo B) or is expected (human Nogo A and Nogo B).

Applicants had provided multiple applications for the antibodies against Nogo proteins without inhibitory activity (see, *e.g.*, Section 2.1 of the Amendment of October 4, 2007). In addition, antibodies that bind to Nogo proteins with and without inhibitory activity can be used in combination with antibodies that are specific for Nogo proteins with inhibitory activity in sequential purification schemes as discussed in the Preliminary Statement of the Amendment of October 4, 2007.

According to M.P.E.P. § 2164.01(c) (Eighth Edition, Rev. 3, August 2005), if any use is enabled, the invention is enabled. As set forth above and in Applicants' previous responses, the application provides enabling support for the use of the claimed Nogo proteins (with or without inhibitory activity) to generate antibodies. The Examiner rejects this argument and contends that the *full scope* of a claim must be enabled. Although Applicants agree that the full scope of a claim must be enabled, Applicants disagree with the Examiner's apparent position that that means every *use* of the claimed composition must be enabled. Where, as here, multiple uses are disclosed, any of the disclosed uses, such as the generation of antibodies, can support a holding of enablement.

Claims 116 and 119 are rejected for lack of enablement although these claims are directed to proteins with more than 95% sequence identity to the proteins that the Examiner found to be enabled. In particular, the Examiner has stated that proteins that are at least 95% identical to protein fragments with demonstrated (rat Nogo A and rat Nogo B) or expected (human Nogo A and human Nogo B) neurite outgrowth inhibitory activity are enabled (Office Action of December 21, 2006, p. 5, first paragraph). Accordingly, at least claims 116 and 119 (specifying more than 95% sequence identity to such proteins) should be found enabled for this additional reason, based on the Examiner's own reasoning.

Claims 135 and 136 are rejected because these claims allegedly encompass proteins without any activity. Without agreeing to the Examiner's contention, Applicants have

amended claims 135 and 136 to recite that the Nogo proteins have one or more specified Nogo functional activities. Claim 141 incorporates the new limitation via its dependency from claims 135 and 136. Claim 138 is rejected because it allegedly encompasses nucleic acids for which no use has been demonstrated. Without agreeing to the Examiner's contention, Applicants have amended claim 138 to recite that the encoded protein has one or more specified Nogo functional activities. As summarized above, and discussed in Applicants' previous responses, the specified Nogo functional activities of binding to or generating antibodies against these proteins is an enabled utility, which is sufficient to satisfy the enablement requirement under 35 U.S.C. § 112.

For the reasons set forth above, the rejections of claims 115-116, 118-119, 123-125, 136, and 138-141 under 35 U.S.C. § 112, first paragraph, for lack of enablement, should be withdrawn.

1.2 THE REJECTION UNDER 35 U.S.C. § 112 BASED ON LACK OF WRITTEN DESCRIPTION SHOULD BE WITHDRAWN

Claims 115-116, 118-119, 123-125, 136, 138, and 141 are rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement. Applicants respectfully disagree as set forth in detail below. Applicants appreciate the Examiner's finding that Nogo proteins that (i) have at least 95% sequence identity to the recited SEQ ID NOs and (ii) have inhibitory activity to be sufficiently described. The Examiner contends that Nogo proteins with lower sequence identity or without inhibitory activity are not sufficiently described.

Applicants respectfully disagree. Applicants had provided evidence in their previous responses demonstrating that all the claimed Nogo proteins are sufficiently described by virtue of disclosed function (namely, antigenicity or immunogenicity) and a known structure-function correlation (namely, hydrophilicity plots that allow for the identification of antigenic/immunogenic regions in the disclosed amino acids sequences of the Nogo proteins). Moreover, as set forth in Applicants' previous responses numerous working examples have been provided. Further, the Examiner is incorrect that Hopp & Woods teaches that any six consecutive amino acids are antigenic. Rather, Hopp & Woods teaches that the point of highest local average hydrophilicity is located in, or adjacent to, an antigenic determinant. See, *e.g.*, Amendment of October 4, 2006, p. 20, Section 2.1.(2).

For the reasons set forth in Applicants previous responses and as summarized above and in response to the enablement rejection under 35 U.S.C. § 112, the rejections of claim 115-116, 118-119, 123-125, 136, 138, and 141 under 35 U.S.C. § 112, first paragraph, for lack of written description, should be withdrawn.

Claim 136, and its dependent claim 141, are rejected under 35 U.S.C. § 112, first paragraph, for lack of written description because these claims allegedly introduce new matter.

Claim 136 has been rejected because allegedly there is no support for fragments at least 95% identical to the recited human Nogo fragments. Applicants disagree, support for these fragments can be found at p. 15, *ll.* 24-26, of the application as filed: "[n]aturally occurring human Nogo and recombinant human Nogo, and fragments thereof having an amino acid sequence substantially similar to the above-described amino acid sequences and able to be bound by an antibody directed against a Nogo protein are within the scope of the invention." It is noted that the "above-described amino acid sequences" include fragments of human Nogo protein (see p. 15, *ll.* 11-12). Human Nogo fragments are specified in claim 136. The term "substantially similar" is defined at p. 15, *l.* 36 to p. 16, *l.* 1, of the specification. In particular, it is stated that an amino acid is deemed to be substantially similar to a Nogo sequence when, *e.g.*, more than 95% of the amino acid residues in the two molecules are identical. Further, the specification discloses at p. 15, *ll.* 31-33, nucleic acids "encoding *fragments* of human Nogo protein having an amino acid sequence substantially similar to the amino acid sequence as shown in Figure 13," *i.e.*, SEQ ID NO:29. Thus, contrary to the Examiner's assertion, this section of the application relates to the Nogo fragments recited in claim 136.

Accordingly, a fragment that is 95% identical to a human Nogo fragment is considered substantially similar to that human Nogo fragment, and such fragments are disclosed (p. 15, *ll.* 31-32). Thus, the skilled artisan could unambiguously derive from this disclosure that Applicants considered proteins with the recited degree of identity as part of the invention.

For the reasons set forth above, the rejection of claims 136 and 141, under 35 U.S.C. § 112, first paragraph, for lack of written description, should be withdrawn.

2. THE PRIOR ART-BASED REJECTIONS SHOULD BE WITHDRAWN

PRIORITY

The Examiner contends that the effective filing date for claim 136, and its dependent claim 141, is September 24, 2001 because the recitation of fragments of human Nogo protein with 95% identity to the amino acid sequence of SEQ ID NO:29 is allegedly new matter. Applicants respectfully disagree.

The present application is the national stage of international patent application no. PCT/US99/26160 filed November 5, 1999, which claims the benefit of U.S. Provisional Application No. 60/107,446 filed November 6, 1998 (the "Priority Application").

Claim 136 has been rejected because allegedly there is no support for fragments at least 95% identical to the recited fragments. These fragments are supported by the application as filed, *i.e.*, PCT/US99/26160 filed November 5, 1999 (35 U.S.C. § 363), for the reasons set forth in Section 1.2 above. Consequently, the effective filing date of the subject matter of claim 136, and its dependent claim 141, is November 5, 1999.

2.1. THE REJECTIONS UNDER 35 U.S.C. § 102 OVER CHEN SHOULD BE WITHDRAWN

Claims 127 and 138 are rejected under 35 U.S.C. § 102(b) as anticipated by Chen *et al.*, 1997 (Society for Neuroscience Abstracts 23:1723; "Chen-1"). The Examiner argues that because Chen-1 discloses cDNA clones that were identified using hybridization screening of a cDNA library with probes based on peptide sequences of a protein with inhibitory activity, these cDNA hybridize to the nucleic acids recited in claim 127 and 138, respectively. The Examiner contends that the recitation of these cDNA clones in Chen-1 constitutes a publication of these cDNA clones within the meaning of the statute. Applicants disagree for the reasons set forth below.

Applicants submit concurrently herewith a Declaration of Prof. Dr. Martin E. Schwab under 37 C.F.R. § 1.132 ("Schwab 2007") to provide evidence that Chen-1 fails to provide the necessary teachings to enable the claimed nucleic acids.

THE LEGAL STANDARD

To be anticipatory under 35 U.S.C. § 102, a prior art reference must be enabling. Although the allegedly anticipatory reference need not provide a utility, the reference must teach a person of ordinary skill in the art to carry out the invention. *See, e.g., Impax v. Aventis*, 468 F.3d 1366 (Fed. Cir. 2006).

Anticipation requires that the same invention, including each element and limitation of the claims, was known or used by others before it was invented by the patentee. *Hoover Group, Inc. v. Custom Metalcraft, Inc.*, 66 F. 3d 299, 302 (Fed. Cir. 1995). An anticipating reference must describe and enable the claimed invention, including all the claim limitations, with sufficient clarity and detail to establish that the subject matter already existed in the prior art and that its existence was recognized by persons of ordinary skill in the field of the invention. *In re Spada*, 911 F.2d 705 (Fed. Cir. 1990); *Crown Operations International, Ltd. v. Solutia Inc.*, 289 F.3d 1367, 1375 (Fed. Cir. 2002).

The standard for an anticipatory reference is set forth in *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987): "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *See also Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989)(holding that "[t]he identical invention must be shown in as complete detail as is contained in the . . . claim"). Further, the anticipating reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter. *PPG Industries, Inc. v. Guardian Industries Corp.* 75 F. 3d 1558 (Fed. Cir. 1996).

CHEN-1 DOES NOT ENABLE THE CLAIMED INVENTION BECAUSE CHEN-1 IS NEITHER A PUBLICATION OF THE NUCLEOTIDE SEQUENCES NOR DID IT MAKE AVAILABLE THE PHYSICAL CLONES

Chen-1 merely states that the listed cDNA clones were obtained. These clones, however, were not made available. Schwab 2007, ¶46. Chen-1 did not disclose the nucleotide sequences of the cDNA clones, Chen-1 did not disclose the amino acid sequences of the peptides of bNI-250, and Chen-1 did not publicly make available the physical cDNA clones. Schwab 2007, ¶46. Further, the names of these clones are not designations to publicly available depositories or databanks. Schwab 2007, ¶46. Thus, even assuming *arguendo*, that the clones that are listed in Chen-1 fall within the scope of claims 127 and

138, Chen-1 is not an anticipatory reference because Chen-1 fails to teach the person of ordinary skill how to obtain these cDNA clones.

As set in more detail below, and as discussed in Prof. Schwab's Declaration, extensive experimentation was required to obtain sequencing-grade Nogo protein, to obtain peptide sequence from that sequencing-grade Nogo protein, and finally to obtain cDNA clones encoding the Nogo protein. Thus, the mere mentioning of cDNA clones for the Nogo gene does not provide an enabling disclosure.

Accordingly, the rejections of claims 127 and 138 under 35 U.S.C. § 102(b) as anticipated by Chen-1 should be withdrawn.

2.2 THE REJECTIONS UNDER 35 U.S.C. § 103(a) OVER CHEN-1 AND SAMBROOK SHOULD BE WITHDRAWN

The rejections of claims 115-116, 118-119, 123-125, 127, 135-138, and 141 under 35 U.S.C. § 103(a) over Chen-1 and Sambrook (1989, Molecular Cloning, pages 16.3 to 16.22 and 17.3 to 17.9; "Sambrook") and Bregman *et al.*, 1995 (Nature 378:498-501; "Bregman") have been maintained. In particular, the Examiner argues that there would have been motivation provided by Bregman to insert the nucleic acids taught in Chen-1 into vectors and host cells and produce proteins, and that these methods were available to the skilled artisan as evidenced by Sambrook. This obviousness rejection is based on the Examiner's conclusion that Chen-1 anticipates claim 127. No further argument is made that the combination of Chen-1 with Sambrook and Bregman makes claim 127 obvious. In fact, the rejection is based on the unsupported assumption by the Examiner that proteins that are at least 90% identical to each other are encoded by nucleic acids that hybridize to each other.

The Legal Standard

In the consideration and determination of obviousness under 35 U.S.C. § 103(a), the Supreme Court in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 10 (1966) stated:

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give

> light to the circumstances surrounding the origin of the subject matter to be patented.

The standard set forth in *Graham* is a broad inquiry which invites looking at any secondary considerations that would prove instructive in the obviousness analysis. *KSR Intern. Co. v. Teleflex, Inc.*, 127 S.Ct. 1727, 1736 (2007). Such secondary considerations include commercial success, long felt but unsolved needs, and failure of others. *Graham v. John Deere*, 383 U.S. 1, 148 USPQ 459 (1966)

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the prior art references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). The reasonable expectation of success must be "founded in the art," and is that of those of ordinary skill in the art. *Id.*

THE CLAIMS ARE NOT OBVIOUS OVER CHEN-1, SAMBROOK, AND BREGMAN BECAUSE THERE WAS NO REASONABLE EXPECTATION OF SUCCESS AND BECAUSE NONE OF THE REFERENCES TEACHES OR SUGGESTS THE STRUCTURE OF THE CLAIMED COMPOUNDS

No Reasonable Expectation of Success

In their previous response, Applicants had provided evidence that there would not have been a reasonable expectation of success that the claimed Nogo proteins and nucleic acids could be obtained from the information provided in Chen-1. The Examiner's attention is further invited to Schwab 2007, wherein it is explained that Chen-1 merely lists the names of several cDNA clones. These names by themselves do not provide any insight into how to obtain the claimed Nogo proteins and nucleic acids because these names do *not* refer to a publicly available depository or databank. Rather, these names are designations that were assigned to these cDNA clones internally in Prof. Schwab's laboratory. Schwab 2007, ¶46.

In the Office Action of December 21, 2006, it is stated that Applicants failed to traverse the Examiner's rejection because Applicants argued that the nucleic acids of Chen-1 were not full length. As discussed in Applicants' previous response and Prof. Schwab's Declaration of October 2, 2006, obtaining the full length cDNAs from the partial sequences

was only part of the difficulty in obtaining Nogo protein and nucleotide sequences. First, sequencing-grade Nogo protein had to be isolated, second, peptide sequences had to be obtained, third, degenerate oligonucleotides designed and synthesized, and, fourth, cDNA libraries screened. As discussed in the currently submitted Declaration by Prof. Schwab (Schwab 2007, *e.g.*, at ¶¶29-40), the purification of sequencing-grade Nogo protein required, as would be expected, extensive experimentation, including trial and error selection among numerous variables for which no guidance was given in the prior art, and thus, there would not have been a reasonable expectation of success. Obtaining the full-length cDNA similarly required extensive experimentation (Schwab Declaration of October 2, 2006, at ¶¶23 and 24).

No Disclosure of the Claimed Structures

Neither Chen-1, Sambrook, or Bregman teaches any of the sequences of the claimed proteins or nucleic acids. In fact, neither Chen-1, Sambrook, or Bregman teach even a partial sequence of Nogo. Accordingly, the mere statement in Chen-1 that certain clones were obtained without any disclosure of amino acid or nucleotide sequence information does not suggest the claimed Nogo proteins and nucleic acids.

It is noted that in *In re Deuel*, 51 F.3d 1552 (Fed.Cir. 1995), the prior art taught relevant peptide sequences. The Court of Appeals for the Federal Circuit nevertheless found the cDNA sequence non-obvious. In the present situation, the prior art does not even disclose peptide sequences. The claimed Nogo proteins free of all CNS myelin material can only be obtained by recombinant means (see, *e.g.*, Schwab 2007, ¶¶8 and 16), *i.e.*, the availability of the Nogo cDNA is a prerequisite for the claimed Nogo proteins. Since the cDNA is not obvious, the Nogo proteins free of all CNS myelin material are also non-obvious.

Thus, the rejections of claims 115-116, 118-119, 123-125, 127, 135-138, and 141 under 35 U.S.C. § 103(a) over Chen-1, Sambrook, and Bregman should be withdrawn.

THE REJECTIONS UNDER 35 U.S.C. § 103 OVER SCHWAB '414 AND SPILLMANN 1995 SHOULD BE WITHDRAWN

Claims 114-119, 123-125, 135, 137, 139, and 141 are rejected under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 5,250,414 ("Schwab '414") as evidenced by Spillmann *et al.* (1995, 27th Annual Meeting of the Swiss Societies for Experimental Biology; Experientia 51:A44)("Spillmann 1995").

THE CLAIMS ARE NOT OBVIOUS OVER SCHWAB '414 AND SPILLMANN 1995 BECAUSE THERE WAS NO REASONABLE EXPECTATION OF SUCCESS AND BECAUSE NONE OF THE REFERENCES TEACHES OR SUGGESTS THE STRUCTURE OF THE CLAIMED COMPOUNDS

Applicants submit concurrently herewith a Declaration of Prof. Dr. Martin E. Schwab under 37 C.F.R. § 1.132 ("Schwab 2007") to provide evidence that none of the cited references, alone or in combination, provides a reasonable expectation of success for the purification of the claimed Nogo proteins or the identification of the claimed Nogo nucleotide sequences.

Preliminary Remark

It is noted that a distinction should be made between Nogo protein that is free of all CNS myelin material (as specified in the instant claims), *i.e.*, pristine Nogo, and Nogo protein that is sequencing-grade. While protein sequencing may still be possible with some minor contaminations with other myelin proteins, pristine Nogo protein requires the absence of *all* CNS myelin material. See Schwab 2007, Footnote 1.

The person of ordinary skill in the art is a hypothetical person with combined experience from different fields of research. To signify this combination, Prof. Schwab refers to the person of ordinary skill as the Molecular Neurochemist. "This combination of experience from different fields of biology contributes to the necessity for more than routine work to obtain pristine Nogo." Schwab 2007, ¶7.

No Reasonable Expectation of Success

In November 1998, the skilled artisan would have had no reasonable expectation of success that a CNS myelin protein of low abundance, such as the Nogo protein, could be purified to such a degree that it could be sequenced, *i.e.*, sequencing-grade Nogo protein, let alone to such a degree that it would be free of *all* CNS myelin material, *i.e.*, pristine Nogo. As stated by Prof. Schwab:

> The Molecular Neurochemist in November 1998 would have expected *complete* separation of all CNS myelin proteins, CNS myelin lipids, and other myelin material from Nogo protein to be virtually impossible by biochemical purification. This is especially true in view of the low abundance of Nogo protein. In fact, we consistently observed that the apparent molecular weight of biochemically isolated sequencing grade Nogo protein, once we were able

> to obtain it, in sodium dodecyl sulfate polyacrylamide gel electrophoresis ("SDS PAGE") (approximately 200 KDa) was significantly above the calculated molecular weight of the conceptually translated protein (approximately 140 KDa). Association of the Nogo protein with lipids that are not eliminated by biochemical isolation steps including the SDS PAGE is the likely explanation for this discrepancy in molecular weight.
>
> In 1998, it was well-known to a Molecular Neurochemist that it was difficult to enrich myelin proteins of low abundance such as Nogo protein to obtain sequencing grade. Even a several thousand fold enrichment from myelin of such a low abundance protein would still be contaminated with other myelin proteins. Especially, contaminations with axonal tubulin were known to hamper the purification of proteins of the CNS because axonal tubulin is highly abundant in CNS protein preparations.
>
> The Molecular Neurochemist further would have expected some difficulty in obtaining sequencing grade Nogo because Nogo was known to be associated with the cell membrane. Most myelin proteins are membrane proteins, and as such most myelin membrane proteins share similar physicochemical properties. However, differences in physicochemical properties among proteins is the basis for the biochemical separation of these proteins from each other. Accordingly, the Molecular Neurochemist would have expected that it would be difficult to separate Nogo from other myelin membrane-associated proteins.

Schwab 2007, ¶¶8-10.

Since the purification of sequencing-grade Nogo protein proved so difficult, the purification of pristine Nogo would have been expected to be even more difficult. Indeed, only the cloning of the Nogo gene provided the means for the generation of pristine Nogo:

> Once the sequence of the Nogo gene was known, Nogo could be expressed recombinantly in cells of choice and therefore would be free of all CNS myelin material. Thus, the Molecular Neurochemist would have expected that the cloning of the gene and recombinant expression of Nogo would have been necessary to obtain pristine Nogo.
>
> In order to identify and isolate the Nogo gene, the skilled person would likely have looked to known methods such as attempting to obtain the protein sequence, synthesizing degenerate probes, and attempting to isolate the relevant cDNA by hybridization. In order to obtain the protein sequence one would have had to first purify Nogo protein to such a degree that protein sequencing was possible, *i.e.*, obtain sequencing grade Nogo. Subsequent to protein sequencing, different degenerate oligonucleotides would be synthesized based on the obtained protein sequence. Because of the degeneracy of the genetic code, these different oligonucleotides would contain only a small fraction of oligonucleotides complementary to the Nogo cDNA. In addition, the isolation of a full-length cDNA could involve overcoming several hurdles, as turned out to be the case (see my Declaration of October 2, 2006).

Schwab 2007, ¶¶15-16.

Schwab '414 does not disclose sequencing grade Nogo protein:

> In Schwab '414, we used conventional biochemical techniques to purify the proteins that are responsible for the inhibitory substrate effect of CNS myelin on neurite outgrowth (see Example 7, at column 42, line 42). Two protein fractions with neurite outgrowth inhibitory activity were obtained by fractionating CNS myelin material using SDS-PAGE. These protein fractions were named NI-35 and NI-250. These protein fractions contained multiple different protein species (see, *e.g.*, column 48, lines 23 to 24 of Schwab '414), and were not sequencing grade Nogo because the contamination with other proteins prevented us from obtaining a useful sequence upon amino acid sequencing.
>
> We generated monoclonal antibodies against NI-250. The monoclonal antibodies were termed IN-1 and IN-2 (see Example 8, column 50, line 8 of Schwab '414). We attempted to use immunoprecipitation using IN-1 and IN-2, respectively, to isolate individual proteins from solubilized CNS myelin protein.
>
> The material immunoprecipitated by IN-1 and IN-2, respectively, was not free of all CNS myelin material natively associated with Nogo protein. When immunoprecipitated proteins were separated by SDS-PAGE, multiple protein bands of molecular weights other than the molecular weights of NI-35 and NI-250 were observed. Thus, the immunoprecipitated material contained myelin proteins other than Nogo protein. Nogo amino acid sequence could not be obtained from the immunoprecipitated material because of this contamination with other proteins.
>
> IN-1 is an IgM which recognizes best the native, membrane-bound Nogo-A protein. Binding of IN-1 to denatured Nogo on Western blots is weak, and some cross-reactivity to CNS myelin material other than Nogo protein was often observed (see Figure 16 of Schwab '414). IN-1 reactive bands of molecular weights other than the molecular weights of NI-35 and NI-250 were observed. Thus, the material that was immunoprecipitated with IN-1 antibody contained myelin proteins other than Nogo protein because of the ability of IN-1 to bind to proteins other than Nogo protein.
>
> IN-2 reacts with neurofilament. In Western blot analysis of CNS material that had been separated by SDS-PAGE, the IN-2 antibody detected a band of the size of neurofilament. Binding of IN-2 to neurofilament was confirmed by Western blot analysis of recombinant neurofilament with IN-2 monoclonal antibody.

Schwab 2007, ¶¶19-23. Spillmann 1995 also fails to disclose sequencing grade Nogo protein:

> The Poster did not present any Nogo sequence information. The poster also did not include the biochemical purification procedure that led later to the

successful purification of sequencing grade Nogo.

In Spillmann 1995, we describe attempts to purify by conventional biochemical techniques the proteins that are responsible for the inhibitory substrate effect of bovine CNS myelin on neurite outgrowth. Crude bovine myelin was subjected to anion exchange chromatography, reverse phase chromatography, size exclusion chromatography, and SDS PAGE.

The procedure described in Spillmann 1995 did not yield sequencing grade Nogo protein, nor did this procedure yield pristine Nogo. Attempts to sequence the protein of the "one detectable band at 250kd" mentioned in Spillmann 1995 did not result in any reproducible sequences because of the presence of a mixture of proteins. Significant experimentation was required to further modify the procedure of Spillmann 1995 to purify Nogo protein to such a high degree that it could be sequenced.

Schwab 2007, ¶¶26-28.

Neither Schwab '414 or Spillmann 1995 provide a reasonable expectation of success that standard biochemical protein purification procedures would result in sequencing grade Nogo protein:

> Based on the purification procedures disclosed in Schwab '414 at col. 18, *ll.* 36-63, the Molecular Neurochemist would not have reasonably expected successful purification of sequencing grade Nogo protein, much less Nogo protein that is free of all CNS myelin material. This lack of expectation is evidenced by the general problems associated with the purification of myelin proteins of low abundance as discussed above. Further, our own attempts to purify Nogo protein, as discussed in more detail below, proved that routine application of standard protocols was insufficient to obtain sequencing-grade Nogo protein, let alone pristine Nogo.

Schwab 2007, ¶24.

> Based on Spillmann 1995, the Molecular Neurochemist would not have had a reasonable expectation that Nogo protein could be purified to sequencing grade. The Molecular Neurochemist would have expected that it would require significant trial and error to obtain enough sequencing grade Nogo for an amino acid sequence determination because many particulars of the purification procedure would have to be custom-tailored and optimized for the Nogo protein. These particulars included protection of Nogo from degradation (*e.g.*, protection from protease digestion), source and treatment of the myelin tissue, extraction conditions (*e.g.*, extraction buffer), number and types of chromatography steps (*e.g.*, optimization of the yield), voltage and duration and type of SDS PAGE, and reconstitution of the Nogo protein after each purification step to perform the bioassays to identify the protein fraction with Nogo activity.
>
> Further, the Molecular Neurochemist would have known that certain biochemical techniques and purification conditions could have unexpected

effects. For example, denaturants and/or detergents to be used during extraction and purification could have unpredictable effects on the protein activity and/or bioassays needed to monitor the purification. This was indeed found to be the case, as described below.

A crucial step for the success of the purification of sequencing grade Nogo protein was the identification of a suitable method to extract proteins from bovine myelin. In particular, the identification of a suitable extraction buffer was challenging. If the buffer is too mild, the extracted protein amounts would be insufficient for subsequent enrichment procedures such as chromatography. If the buffer is too strong, on the other hand, it would interfere with the bioassay, which is an essential step during the purification procedure to identify the Nogo-containing fractions. In particular, remaining detergent or denaturant in the buffer could be toxic to the cells in the NIH 3T3 fibroblast spreading assay and the PC12 cell neurite outgrowth assay. Thus, we were confronted with the task to identify a buffer that would provide the optimal balance between amount of extracted protein and toxicity in our bioassay.

Initially, we tested extraction buffer containing SDS. The remaining SDS in our protein fractions proved toxic to the NIH 3T3 fibroblasts and the PC12 cells. We also tested a urea-based buffer. The results with this buffer were similarly unsatisfactory and unreproducible. After several other failed attempts, the combination of homogenization in CHAPS buffer with centrifugation at 100,000 x g provided material suitable and in sufficient amounts to purify Nogo protein. I am not aware of any publication prior to our own published data in Spillmann *et al.*, 1998 (J. Biol. Chem. 273:19283-19293; attached as Exhibit 8) that suggested to use this extraction method for the purification of Nogo protein.

Spillmann 1995 disclosed the use of reverse phase chromatography. We tested C4 columns for reverse phase chromatography. However, we ultimately discontinued the use of C4 columns because the protein yield with these columns was too low for further processing, such as subsequent enrichment and/or protein sequencing. It was only by significant experimentation that we realized that the use of reverse phase chromatography was unsuitable for the purification of Nogo protein.

The last step of the Nogo purification described in Spillmann 1995 included the use of SDS PAGE. This step of SDS PAGE was ultimately used in a successful purification procedure to obtain sequencing grade Nogo protein. To identify the Nogo containing bands, we cut out bands from the SDS gel and extracted the proteins. These proteins had to be tested for their inhibitory activity in our bioassay to verify the presence of Nogo. However, as discussed above, SDS interferes with our bioassay. We surprisingly found that the CHAPS extraction buffer was suitable for eluting the proteins from the gel and to eliminate the SDS.

Further, with regard to the SDS PAGE step, the running time proved to be crucial. Only by running large amounts of proteins on SDS slab gels for about one day at low voltage, were we able to obtain sufficient sequencing-grade

material. Other SDS PAGE approaches that we tested included gradient SDS PAGE and two-dimensional gel electrophoresis. However, these approaches proved unsuccessful in providing sequencing grade Nogo protein.

Nogo's instability also hampered our attempts to obtain sufficient sequencing-grade material. In order to minimize protein loss, we went directly to the slaughterhouse where we obtained fresh bovine spinal cords and froze them in liquid nitrogen as soon as the material was made available to us. Surprisingly, we found that freeze/thaw cycles, although detrimental to some proteins, were not damaging to Nogo.

An additional parameter that required significant experimentation was the identification of the most effective combination of protease inhibitors. After different protease inhibitor cocktails were tested, a mixture of iodacetamide, phenylmethylsulfonyl fluoride, aprotinin, leupeptin, and pepstatin A proved to protect Nogo sufficiently from myelin proteases to obtain sufficient amounts of sequencing-grade material.

We also noticed that it was essential to test the protein fractions during the isolation procedure not only for their inhibitory activity, but also to confirm that the inhibitory activity could be neutralized by the IN-1 antibody because several other, non-Nogo containing protein fractions, also had inhibitory activity, which could not be neutralized using IN-1 antibody.

Ultimately, the combination of CHAPS extraction buffer, anion exchange chromatography (Q-Sepharose), size exclusion chromatography (Superdex 200), SDS PAGE and reconstitution in CHAPS buffer, and repeated identification of the Nogo-containing fractions by bioassays and IN-1 neutralization led to the successful production of sequencing grade Nogo protein in sufficient amount for successful sequencing.

As discussed above, based on Schwab '414 and Spillmann 1995, the Molecular Neurochemist would have expected that significant experimentation with uncertain outcomes would be required in an attempt to obtain sequencing grade Nogo protein, thus negating any reasonable expectation of success in achieving sequencing grade Nogo protein. The combination of these two references does not change this situation. In fact, the general biochemical purification procedures taught in these two references provide at best a general direction for future experimentation to obtain sequencing grade Nogo protein. But the combination of these references also fails to provide any of the particulars that were necessary to obtain sequencing grade Nogo protein.

Schwab 2007, ¶¶29-40.

Secondary Considerations: Failure of Others

During the long time that passed between the initial discovery that proteins in the myelin of CNS have inhibitory activity, or even the development of an antibody that

neutralized that inhibitory activity, see, *e.g.*, Caroni and Schwab, 1988, Neuron 1:85-96,[4] and the cloning and molecular characterization of Nogo as described in the present application, other research groups failed at cloning the Nogo gene:

> From the early 1990's on, competing research groups tried to purify and clone Nogo protein. None of these attempts were successful. I am aware of two failed attempts to purify Nogo protein that are documented in the literature. These attempts are described in the following paragraphs.
>
> The laboratory of J.D. Steeves in Vancouver reproduced our neurite growth inhibition data in the chicken embryo, showing that the end of the regeneration permissive period coincides with myelination (Keirstead, PNAS 89, 1992:11664-8; attached as Exhibit 2). Dr. Steeves and his group subsequently attempted to purify and characterize the relevant myelin associated growth inhibitory proteins. A first report was published in 1993 (Ethell, Dev. Brain. Res. 76, 1993:163-9; "Ethell;" attached as Exhibit 3). In Ethell, only several isoforms of the highly abundant ovalbumin protein were characterized. Subsequent attempts to isolate and characterize neurite-outgrowth-inhibitory proteins from chicken myelin in Dr. Steeves' laboratory were not successful and ultimately were discontinued. [FN3] In particular, the scarcity of these proteins in myelin material was likely responsible for the lack of success. [FN4]
>
> The laboratory of Peter Braun at McGill likewise attempted to purify and characterize the proteins that mediate the inhibitory activity of myelin. In McKerracher et al. (Neuron 13, 1994:805-811; attached as Exhibit 4), the purification of two main inhibitory fractions from CNS myelin is described. One of these fractions contained Myelin-Associated Glycoprotein; the other fraction contained a high molecular weight protein, which was believed to be Nogo, or in the words of the authors: "[the] likely candidate is one of the myelin proteins recognised by the IN-1 antibody that have been partially characterised by Schwab and collaborators . . . ." None of the many papers published by the Braun laboratory since then describes the further purification of Nogo. Personal communications between me and Dr. Braun confirmed that the efforts of the Braun laboratory to further purify Nogo protein failed.
>
> In fact, the isolation of sequencing grade Nogo protein by my laboratory, and our report of the sequence thereby obtained, has been described as a "breakthrough" by other scientists in the field, that made it possible to clone the Nogo gene (Goldberg and Barres, 2000, Nature 403:369-370 (middle column, first full sentence); attached as Exhibit 5; see also Tessier-Lavigne and Goodman, 2000, Science 287:813-814; attached as Exhibit 6).

FN3 I was aware of the progress in Dr. Steeves' laboratory because of personal communications between him and me.

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[4] This reference was submitted as reference "CA" in the Information Disclosure Statement of March 19, 2003.

FN4 Personal communications between Dr. Steeves and me.

Schwab 2007, ¶¶11-14.

Thus, failures of others when attempting to achieve the claimed invention is objective evidence of its non-obviousness. See *Graham v. John Deere*.

No Disclosure of the Claimed Structures

Neither Schwab '414 or Spillmann 1995 teaches or suggests any of the sequences of the claimed proteins or nucleic acids. In fact, neither Schwab '414 or Spillmann 1995 teaches or suggests even a partial sequence of Nogo.

Accordingly, the rejections of claims 114-119, 123-125, 135, 137, 139, and 141 under 35 U.S.C. § 103(a) as obvious over Schwab '414 as evidenced by Spillmann 1995 should be withdrawn.

THE DOUBLE PATENTING REJECTION OVER SCHWAB '133 SHOULD BE WITHDRAWN

Claims 114-119, 123-126, 135, 137, 139, and 141 are rejected on the ground of non-statutory obviousness-type double patenting over claims 2-3 of U.S. Patent No. 5,684,133 ("Schwab '133"). In particular, the Examiner contends that the requirement that the currently claimed Nogo proteins be free of all CNS myelin material does not provide a patentable distinction over the claim term "essentially purified and isolated" of claims 2 and 3 of Schwab '133. Applicants disagree for the reasons set forth below.

LEGAL STANDARD

The standard for determining whether an obviousness-type double patenting rejection is proper is whether:

> [A] person of ordinary skill in the art would conclude that the invention defined in the claim in issue is an obvious variation of the invention defined in a claim in the patent. When considering whether the invention defined in a claim of an application is an obvious variation of the invention defined in the

> claim of a patent, the disclosure of the patent may not be used as prior art. (Emphasis added).

See M.P.E.P. 804(II)(B)(1). "[A]ny analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. § 103 obviousness determination." See M.P.E.P. 804(II)(B)(1).

The specification of the patent underlying the double patenting rejection cannot be used as a reference under 35 U.S.C. 103. *In re Vogel*, 422 F.2d 438, at 925 (CCPA 1970).

THE CLAIMS ARE NOT OBVIOUS OVER CLAIMS 2 AND 3 OF SCHWAB '133 BECAUSE THERE WAS NO REASONABLE EXPECTATION OF SUCCESS AND BECAUSE THE STRUCTURE OF THE CLAIMED COMPOUNDS WERE NOT DISCLOSED OR SUGGESTED BY THESE CLAIMS 2 AND 3

Schwab '133 enables and describes "essentially purified and isolated Nogo protein." However, in view of the methods for protein purification that were available at the time, the skilled artisan would not have had a reasonable expectation of success to purify Nogo protein to such a degree that it could be sequenced, *i.e.*, sequencing grade Nogo protein, let alone Nogo protein free of all CNS myelin material, *i.e.*, pristine Nogo protein:

> As discussed above, the Molecular Neurochemist would not have expected that sequencing grade Nogo protein, much less pristine Nogo protein, could be obtained even where significant enrichment was already known because of the difficulties associated with the complete elimination of other myelin materials, including proteins, lipids, and other materials. Further, the Molecular Neurochemist would have expected that significant difficulties would be associated with selecting from among the many variables the particular procedures necessary to obtaining sequencing grade material: achieving protection of Nogo from degradation (*e.g.*, protection from protease digestion), determining source and treatment of the myelin tissue, determining extraction conditions (*e.g.*, extraction buffer), determining number and types of chromatography steps (*e.g.*, optimization of the yield), determining voltage and duration and type of SDS PAGE, and achieving reconstitution of the Nogo protein after each purification step to perform the bioassays to identify the fraction with Nogo activity. The foregoing was not straightforward, as evidenced by our own experience described above in the discussion of Spillmann 1995.

Schwab 2007, ¶43.

Thus, the essentially purified and isolated Nogo proteins of claims 1 and 2 of Schwab '133 do not render obvious the "pristine" Nogo proteins and related molecules of the rejected claims.

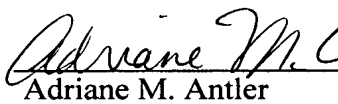
Accordingly, the rejections of claims 114-119, 123-126, 135, 137, 139, and 141 on the ground of non-statutory obviousness-type double patenting over claims 2-3 of Schwab '133 should be withdrawn.

CONCLUSION

Applicants respectfully request that the present remarks and amendments be entered and made of record in the instant application. An allowance of the application is earnestly requested. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

Date: June 21, 2007



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